III. REMARKS

Claim Status

Claims 1-40 are in the application; claims 1-29 stand rejected; claims 1-28 have been amended, claims 30-40 are newly presented.

The subject-matter of claim 1 has been amended to include the limitations of former claim 9, i.e. in that the dosage form as such exhibits a breaking strength of at least 500 N. Former claim 9 has been deleted accordingly.

The dependency of former claim 13 (on claim 1) has been corrected (on claim 11).

In claim 16 the typographical error " t3-asarone" has been corrected to "ß-asarone" (cf. present application, page 16, line 20).

The trademarks have been deleted from claim 17.

In all remaining claims the expression "characterized in that" has been replaced by the terms "wherein" and "which", respectively.

The present invention

The following short summary of the concepts underlying the present invention will help to demonstrate its novelty and unobviousness over the prior art.

In most cases of abuse it is necessary to pulverize the dosage form comprising an active ingredient suitable for abuse. It is the object of the present invention to complicate or prevent the pulverization of the dosage form preceding abuse and accordingly to provide a dosage form for active ingredients with abuse potential which ensures the desired therapeutic effect when correctly administered, but from which the

active ingredients cannot be converted into a form suitable for abuse simply by pulverization (Specification, page 2, line 32 to page 3, line 9).

This object has been achieved by providing a dosage form exhibiting a minimum breaking strength of at least 500 N, as set forth in amended claim 1.

The attendant difficulties in pulverizing the dosage form using conventional means makes it much harder to abuse the active ingredient. If comminution is inadequate, parenteral, in particular intravenous, administration cannot be performed safely or extraction of the active ingredient therefrom takes too long for the abuser or there is no "kick" when taken orally, as release is not spontaneous (Specification, page 3, lines 19-30).

According to the invention, comminution means pulverization of the dosage form with conventional means which are available to an abuser, such as, for example, a mortar and pestle, a hammer, a mallet or other usual means for pulverization by application of force. The dosage form according to the invention is thus suitable for preventing parenteral, nasal and/or oral abuse of pharmaceutical active ingredients with abuse potential (Specification, page 3, line 32 to page 4, line 7).

The dosage forms according to the invention are distinguished in that, due their hardness, they cannot be pulverized, for example by grinding in a mortar. This virtually rules out oral or parenteral, in particular intravenous or nasal abuse (Specification, page 12, lines 4-8).

Summing up, the inventive concept of the present invention does not primarily rely on the presence of aversive agents, antagonists and the like. Such additives do not have to be present in order to solve the problem posed.

The inventive concept underlying the subject invention is rather concerned with the mechanical properties of the dosage form as such, particularly its breaking strength. these mechanical properties prevent the dosage form from being suitable for abuse.

In this regard it should be emphasized, however, that the mechanical properties of the dosage form according to the invention may not automatically be achieved by simply processing components (A), (C), optionally (B) and optionally (D) by means of conventional methods for the preparation of pharmaceutical dosage forms.

The importance of this point is highlighted by the fact that apparatus used for preparation of the dosage forms must be selected and critical processing parameters must be adjusted, particularly pressure/force, temperature and time. The inventive dosage forms exhibiting the desired properties may be obtained only if, during preparation of the dosage form, the components are exposed to a sufficient pressure at a sufficient temperature for a sufficient period of time. Thus, regardless of the apparatus used, the process protocols must be adapted in order to meet the required criteria.

The experimental section of the present application exemplifies preparation of the dosage forms according to the invention, e.g., by means of a tabletting tool. The mixture of components (A) and (C) is heated to a temperature in the range of 80 to 90°C, which is above the softening temperature of component (C). The heated powder mixture is then pressed with the heated tool, wherein pressure is maintained for at least 15 seconds by clamping the tabletting tool in a vice.

In contrast, conventional processes for the manufacture of dosage forms, such as compressing a mixture of all components at room temperature for less than 1 second, fails to provide dosage forms exhibiting a breaking strength of at least 500 N.

Claim Rejections* - 35 *USC* § *112, second paragraph

Claim 17 contains various trademarks/trade names which when used to identify/describe a component render the claim indefinite. The claims have been amended to remove the trademarks/trade names thus obviating this ground for rejection.

Claim Rejections* - 35 *USC* § *102

Claims 1-11, 18, 21 and 23-29 stand rejected under 35 U.S.C. 102(b) as being anticipated by Alaux et al.(WO/002000/033835).

Applicant traverses this ground for rejection.

Alaux et al. (WO 00/33835) relates to controlled-release forms of zolpidem, a hypnotic, according to a biphasic profile of dissolution.

Alaux et al., discloses that one technique for substantially reducing or eliminating the potential for drug abuse is to provide pharmaceutical compositions for oral administration comprising zolpidem which

- liberate the active principle according to a biphasic in vitro profile, following normal administration and,
- if introduced in a drink, generate visual changes in the appearance of the drink.

The visual changes are intended to avoid administration of the active principle to a person in the drink without his or her knowledge (*Alaux et al.*, page 12, line 34 to page 13, line 8). These visual changes include all means of indicating the presence of the composition in a drink, such as inclusion of coloring excipients, floatation of the composition at the surface of the drink, formation of insoluble particles on the surface of the drink, on the brim of the glass, in the drink and/or on the bottom of the glass or a combination thereof (*Alaux et al.*, page 13, lines 10-17).

Therefore, *Alaux et al.* discloses the concept of avoiding abuse based on visual changes which appear when the dosage form is used improperly, e.g. dissolved in a drink.

As *Alaux et al.* does not disclose a dosage form having a breaking strength of at least 500 N, either explicitly or implicitly, the subject-matter of amended claim 1 has not been anticipated. Favorable reconsideration is requested.

Claims 1-6, 9-11, 17, 18, 21 and 23-29 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kuczynski et al. (US 5,866,164).

As stated by the examiner, Kuczynski et al. teaches of a composition comprising an opioid, an opioid antagonist and a high molecular weight poly(alkylene) or a poly(carboxymethylcellulose (Abstract). An antagonist composition contains a polyethylene oxide of 7,000,000 (or 3,000,000 to 15,000,000) molecular weight, naloxone and ferric oxide which is granulated, pressed and coated (column 2, lines 56 et seq.; column 8, line 16).

Kuczynski et al. discloses a dosage form comprising an opioid composition and an antagonist composition which are separate and distinct from one another (*Kuczynski et al.*, column 2, lines 27-30). Both compositions are pressed in a standard tablet press into a bilayered core, with the opioid composition and the antagonist composition in bilayered arrangement (*Kuczynski et al.*, column 2, line 64 to column 3, line 3; column 3, line 64 to column 4, line 1). Said bilayered core is coated with a semi-permeable membrane, permeable to aqueous-biological fluid and impervious to an opioid (*Kuczynski et al.*, column 3, lines 5/6; column 4, lines 8/9; column 8, lines 9/10). Exit passageways are drilled through the membrane to connect the opioid drug layer with the exterior of the dosage form (*Kuczynski et al.*, column 3, lines 11-14; column 4, lines 15-18).

The exit means in the wall are for delivering the opioid from the dosage form by imbibing fluid through the wall into the dosage form, causing the opioid composition and the antagonist composition to expand and push the opioid drug composition through the exit means, whereby through the combined operations of the dosage form, the opioid analgesic is delivered at a therapeutically effective dose at a controlled rate over a sustained period of time. The dosage forms allows the administration of an opioid analgesic to a patient while simultaneously maintaining an opioid antagonist in the dosage form to prevent opioid abuse (*Kuczynski et al.*, column 8, lines 23-35).

Therefore, *Kuczynski et al.'s* disclosure is based on the presence of an opioid antagonist which neutralizes the pharmaceutical efficacy of the opioid when the dosage form is used improperly, but which remains passive when the dosage form is administered in accordance with the prescription.

As *Kuczynski et al.* does not disclose a dosage form having a breaking strength of at least 500 N, either explicitly or implicitly, the subject-matter of amended claim 1 has not been anticipated. Favorable reconsideration is requested.

Claims 1-13, 16-18 and 21-29 stand rejected under 35 U.S.C. 102(e) as being anticipated by Oshlack et al. (US 2003/0064099A 1).

As stated by the examiner, Oshlack et al. teaches an oral dosage form of an opioid analgesic with reduced abuse potential due to the addition of an aversive agent, such as a bittering agent that provides buming or irritating effects. A gelling agent, such as microcrystalline cellulose or polyethylene oxide can also be used to reduce the absorption of the opioid analgesic through injection when the dosage form is tampered with.

Polyalkylene oxide molecular weights vary from 1,000,000 to 10,000,000. The dosage form may be a sustained release form in a matrix with the aversive agents including peppermint oil, oil of bitter almonds, capsaicin, as well as those listed in the instant claims. Suitable controlled release tablets may be formulated from multiparticulate formulations, wet granulation that is compressed into a tablet or melt and may contain hydrophobic binders, such as carnauba wax.

Oshlack et al. discloses an oral dosage form comprising an aversive agent such as a bittering agent, an irritant or a gelling agent to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form.

Preferably, the aversive agent is released when the dosage form is tampered with and provides an unpleasant taste, a burning or irritating effect, and a gel-like quality, respectively (*Oshlack et al.*, 0021-0023). The term "tampered dosage form" is defined to mean that the dosage form has been manipulated by mechanical, thermal, and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding and chewing (*Oshlack et al.*,0031).

Thus, *Oshlack et al.'s* disclosure is based on the presence of an aversive agent which is released when the dosage form is comminuted, e.g. crushed, sheared, ground or chewed.

As *Oshlack et al.* does not disclose a dosage form having a breaking strength of at least 500 N, either explicitly or implicitly, the subject-matter of amended claim 1 has not been anticipated. Favorable reconsideration is requested.

Claim Rejections* - 35 *USC* § *103

Claims 1-29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alaux et al. (WO/2000/033835) in view of the combined disclosures of Oshlack et al. (US 2003/0064099A 1), Porter (US 4,175,119) and Miller et al. (US 5,849,240).

Alaux et al. and Oshlack et al. are discussed above.

Porter discloses a composition and method of inducing emesis to preclude death from accidental or intentional overdose of a therapeutic composition. The surface of the therapeutic composition is coated with an emetic chemical of such quantity that if the therapeutic composition is consumed in a moderation or in accordance with the prescription, no emesis occurs; but if consumed excessively and not in accordance with

the prescription, emesis results to render the therapeutic composition harmless and precludes death or serious illness (*Porter*, abstract).

Hence, *Porter's* disclosure is based on the presence of an emetic chemical which causes vomiting when the dosage form is consumed in excessive amounts.

Miller et al. discloses a process for the manufacture of particles comprising mechanically combining a mixture of a drug and a hydrophobic and/or hydrophilic fusible carrier in a mixture so as to form agglomerates and thereafter breaking the agglomerates to give controlled release particles (*Miller et al.*, Abstract). *Miller et al.* relates to a different technical field and is not concerned with the avoidance of drug abuse.

In summary, *Miller et al.* relates to non-analogous art and *Alaux et al.*, *Kuczynski et al.*, *Oshlack et al.* and *Porter* rely on conventional concepts for the avoidance of drug abuse, such as have been described on page 2 in the introductory part of the present application.

The examiner states that at the time of the invention it would have been obvious to one ordinarily skilled in the art to combine the oral dosage form of Alaux et al. with the antiabuse formulations of Oshlack et al. or emetic formulation of Porter to make a safe abuse-proof dosage form that when taken properly will not exhibit the emetic or bitter characteristic. The use of the neuroleptic rather than an opioid agonist would be obvious to produce an antipsychotic abuse-proof dosage form for treatment of schizophrenia or mood disorders.

The examiner's statement that all of the disclosed formulations have similar excipients and coatings and would be considered interchangeable has been demonstrated by applicant in his application to be incorrect. To the extent that one skilled in the art might consider them interchangeable, absent knowledge of applicants compositions exhibiting a breaking strength of at least 500N and the means to obtain such dosage forms, this would further demonstrate the unobviousness of applicants dosage forms.

None of the references, taken alone or in combination, disclose or suggest the instant solution to the abuse problem, that of providing a dosage form that is highly difficult to comminute, nor do they describe a technique for obtaining such an abuse resistant dosage form.

None of the cited prior art references contain any hint that drug abuse may be avoided by providing a dosage form with a particular breaking strength, let alone with a breaking strength of at least 500 N. The cited prior art references do not even contain any hint as to how dosage forms exhibiting a breaking strength of at least 500 N may be manufactured.

Therefore, the subject-matter of new claim 1 cannot have been rendered obvious by any of these references, neither when taken alone, nor when combined with one another.

Applicant respectfully suggests the examiner has not made out a *prima facie* case and requests favorable reconsideration.

Conclusion

It is respectfully submitted that all of the claims present in the application are novel and patentable, and are in proper form for allowance. Accordingly, favorable consideration and allowance is respectfully requested. Should any unresolved issues remain, the Examiner is invited to call Applicants' attorney at the telephone number indicated below.

The Commissioner is hereby authorized to charge payment of $120.00 for the one month extension of time fee and $500.00 for the extra claims fee as well as any other fees associated with this communication or credit any over payment to Deposit Account No. 16-1350.

Respectfully submitted,

27 November 2006
Date

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